ILLUSTRATIVE CASES OF MYELOGENOUS LEUKEMIA.—PRELIMINARY REPORT.*

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IT IS the object, in this paper, to present a history of three cases of this disease, and to call particular attention to the treatment which has been, and is being, carried out in two of them.

Case 1. R. R., was admitted to the medical service of St. Luke's Hospital, October 18, 1903. Male, age 61; family history negative. History: He denied venery; had had typhoid and influenza, the latter three or four times. Ten years ago he slipped and "strained his left side," and has had some soreness in the region ever since. For three years he has been troubled with frequency of urination. For the past three weeks he has been getting weaker, and is now suffering from dyspnea and cyanosis.

He appears fairly well developed and nourished. His right eye is artificial, the left reacts normally. His tongue is slightly coated. Pulse is 136, regular, equal, low tension, small volume. Arteries are sclerotic. Heart outline is obscured by surrounding dulness. Apex beat is heard with maximum intensity at the end of the sternum. A soft systolic murmur is heard at the end of the sternum and right second interspace. Sounds are rapid and weak. Right lung is hyperresonant, vocal fremitus and breath sounds exaggerated. Left lung is dull throughout its entire area except supra- and infra-clavicular, and supra-scapular regions. Vocal fermitus is lost and vocal resonance much decreased over entire dull area. The abdomen is prominent; a tumor is palpable continuous with splenic cardiac and pulmonary dulness, filling left side of abdomen and extending well over into the right superior and inferior quadrants. Feet are somewhat swollen and edematous. Prostate gland is enlarged. Catheterization immediately after urination obtained only a few drops of highly colored urine with a thick sediment. The urine was acid, with a sp. gr. of 1022; no sugar, a trace of albumen, the sediment consisting of amorphus urates, hyaline and granular casts, uric acid crystals, and some squamous epithelial cells. A blood examination revealed 3,860,000 red cells, hemoglobin 75%, leucocytes 45,400, of which 55% were polymorphonuclear neutrophiles, 13% lymphocytes, 25% myelocytes, 7% eosinophiles; no nucleated red cells, no poikilocytosis.

Magnesium sulfate was administered, strychnin and digitalis given, and hot compresses applied over the bladder to relieve the pain and tenesmus with which he suffered. Anuria became a distressing and prominent feature, and repeated catheterization being futile, the encroachment of the tumor mass in the pubic region making it impossible to tell whether or not the bladder contained urine, hypodermoclysis of salt solution was resorted to, which was followed by voluntary and fairly copious urination. On Oct. 25, the leucocytes had increased to 89,400, of which 57% were polymorphonuclears, 6% lymphocytes, 10% eosisophiles, 27% myelocytes, with a few normoblasts visible.

Oct. 27. The morning of the day he died, the red cells numbered 4,130,000, hemoglobin 70%, leucocytes 98,000; polymorphonuclears 59%, lymphocytes 11%, melocytes 27%, eosinophiles 3%. Since his entrance dyspnea has been a constantly distressing symptom, his respiration ranging from 26 to 40, his pulse from 100 to 136. The entire course was afebrile. He became progressively weaker from the time of his admission, and died on the evening of October 27.

Autopsy: The liver weighed 2,430 grammes. The cut surface was of a pale brownish color; consistency rather soft. Microscopically the capillaries were everywhere dilated, and contained great numbers of leucocytes, especially myelocytes. The liver cells contained a small amount of brown pigment.

The lungs weighed 276 and 253 grammes respectively. They showed moderate anthrocosis and the cut surface was somewhat edematous. Microscopic sections showed distention of the capillaries of the trabeculae which were filled with blood and showed many white cells, especially myelocytes.

The heart weighed 360 grammes. It was large, pale and flabby; both auricles and ventricles contained postmortem clots.

The kidneys weighed 148 and 153 grammes respectively; the pelves and ureters were much dilated. The pelves contained a number of adherent antemortem clots, with a quantity of brownish semi-fluid material. The cortex was diminished on both sides; the capsule adherent in spots. On section were seen many good-sized areas in the cortex consisting of cellular connective tissue; in many places the connective tissue stroma of the cortex was increased; also there were areas in which the tubules had entirely lost their lining epithelium and were filled with coagulated fluid. In other places the epithelium of the tubules showed necrosis and disintegration.

The spleen weighed 2,430 grammes; its capsule was thickened and its substance very soft and friable. Microscopic section showed many areas of intense hyperemia under the capsule. The spleen substance was heavily infiltrated with myelocytes; in spots there was some brown pigmentation of the cells of the spleen pulp.

No examination was made of the bone marrow.

Case 2. Mrs. B. was referred to me by Dr. H. M. Sherman, October 9, 1903. Age 29, born in Tennessee. Family history unimportant. She has always led an out-of-door life. She had scarlet fever when a child, and when 12 or 13 years of age had malaria. She lived in Tennessee and Kentucky before coming to California a few years ago. She has not felt well since her last child was born five years ago. Menses always normal, except the month before coming to me, when she had menorrhagia. One year ago she noticed a swelling in her abdomen, and has grown continuously weaker. In appearance she is tall, looks pale, and more than the stated age.

Physical examination: There is prolonged expiration at the apices of both lungs posteriorly. The heart boundaries are at the third rib above, two cm. inside the mammary line at the left, and four and one-half cm. from the sternum at the right. A soft systolic murmur is heard, most distinctly at the pulmonic orifice, and the second pulmonic sound is much accentuated.

The abdomen presents a full rounded prominence occupying the left superior and inferior, and right inferior quadrants. Splenic dullness extends up to the seventh rib. A dull mass continuous with splenic dulness extends to a distance of 7 cm. below a transverse line drawn through the umbilicus, and 6 cm. to the right of the median line. The liver is not enlarged downward, its upper border is at the fifth rib. This mass is tender on palpation. The veins of the legs are distended, and there are ecchymotic spots on the body.

Blood examination showed red cells 4,200,000, hemoglobin 60%, leucocytes 240,000 of which 70% were polymorphonuclear neutrophiles, 8% lymphocytes, 20% myelocytes, and 2% were eosinophiles; two nucleated red cells were seen; no poikylocytosis.

A diagnosis of myelogenous leukemia was made. Fowler's solution in increasing doses was prescribed, and husband informed of the grave and heretofore hopeless prognosis. Senn having reported a case successfully treated by the X-ray (*Medical Record*, Aug. 22, 1903) this treatment was begun with this patient, October 19, the splenic tumor being exposed to rays emanating from a medium high vacuum tube, at an average distance of 10 inches, for from 15 to 20 minutes daily. October 24, after six treatments, the splenic mass had decreased 2 cm. in its transverse measurement, and the leucocytes had decreased to 132,000. The patient felt better, but complained of considerable thirst since the beginning of treatment. November 5 she complained of chills, fever, and anorexia, and had been coughing for three days. There was dulness at the right apex, and faint mucous rales over both apices behind. Temperature was 100.4°, pulse 94. Rest in bed and appropriate treatment was instituted. No tubercle bacilli were found in her sputum. She recovered uneventfully and X-ray treatments were resumed after a lapse of ten days. Fowler's solution was at this time discontinued.

Dec. 11, the leucocytes numbered 100,800 (with a differential count as follows: polymorphonuclear neutrophiles 52%, lymphocytes 1%) myelocytes 41%, eosinophiles 6%; one nucleated red cell was seen. The spleen was felt 2 cm. to the right of the umbilicus.

Jan. 11, 1904, the leucocytes had decreased to 80,000, the myelocytes being only 27%; and on February 11, the leucocytes numbered 77,000 with a relative count of myeloctes of only 15%, many of them having a large indented nucleus. There were 4% of eosinophiles, some of which were eosinophilic myelocytes. There was no change in the number of red cells. The spleen extended only to the median line, and below to a distance of 6 cm. below the umbilical line in the left inferior quadrant.

March 11, the red cells had decreased to 3,500,000, hemoglobin 60%, and the leucocytes had increased to 117,500 (with polymorphonuclears 58%, small lymphocytes 3%, large lymphocytes 5%) myelocytes 33%, (and eosinophiles 1%); a few nucleated red cells were seen. At this time the patient complained that for the last two weeks she had been having chills, occasional attacks of vertigo, headache, and loss of appetite, with considerable tenderness on pressure over the spleen. Treatments were temporarily stopped, she was put to bed, and the apparent toxemia treated with cathartics and small doses of strychnin. At this time an examination of the spleen showed some enlargement; it extended 4 cm. to the right of the median line, and 3½ cm. below the umbilical line at its lowest point. This condition lasted a week, during which time there was a slight febrile reaction (the temperature reaching 99.5°).

March 19, X-ray treatments were resumed and have progressed without interruption to the time of writing. April 1, a blood examination showed 3,680,000 red cells, hemoglobin 70%, leucocytes 88,000; polymorphonuclears 64%, small lymphocytes 5, large lymphocytes 4%, myelocyte 21%, transitionals 4%, eosinophiles 2%, an occasional nucleated, red cell was seen. This differential count, as the others, was based on a count of more than 500 cells.

*Read at the Thirty-fourth Annual Meeting of the State Society, Paso Robles, April 19-21, 1904.

Her spleen was felt in the median line, and was about 5 cm. below the umbilical line. She says she feels well, her appetite is good, and she has lost the worn look.

From the beginning of treatment to April 1, she received 125 X-ray treatments, averaging 17½ minutes for each exposure. There were four intervals when treatment was suspended for ten, two, five, and seven days respectively. On a few occasions a slight reddening of the skin over the exposed part was noticed, but aside from that there was nothing but the characteristic bronzing. The increase in leucocytes and the decided increase in both the relative and actual number of myelocytes, together with the increased size of the spleen, noticed March 11, is interesting. A number of the exposures immediately preceding that date had been made with a tube of a lower vacuum, and consequently producing rays of less penetration. This error in technic has, of course, been corrected. Also at this time the patient had considerable mental worry, which had produced sleeplessness. The febrile attack which she had in March was probably a toxemia due either to the absorption of the hyperplastic splenic tissue or to some intercurrent infection.

The urine, which was examined from time to time, presented nothing interesting except a faint trace of albumen.

Case 3. S. H., seen in consultation with Dr. F. W. Simpson of San Francisco. This patient was a male, aged 60, a mechanic, born in Canada. Family history, habits and previous history unimportant.

About fifteen months ago he began to have a tired feeling toward evening, which continued to increase, accompanied by a general weakness. Three months later he began to notice slight edema of the ankles in the evening. About this time he complained of fulness and discomfort in the epigastric region, especially after eating. He next noticed a bronzing of the skin, especially the exposed parts. He was first seen by Dr. Simpson in November, 1903. He was of ordinary stature, medium development, poorly nourished, with dry skin. Temperature 97.8°.

His lungs were normal. Cardiac areas were normal; a hemic basal murmur was present. There was edema of both lower extremities. The abdomen was distended; liver slightly enlarged; spleen enlarged downward, extending through the left hypochondrium into the left lumbar and umbilical regions to within 3¾ cm. of the umbilicus.

Dec. 22, urinalysis showed acid reaction, sp. gr. 1,020, urea, .015%, a trace of albumen, a few hyaline casts, mucus strips, a few white blood cells, and amorphous urates.

Blood examination at the same time showed red cells 2,450,000, hemoglobin 50%, and leucocytes 250,000, of which 51% were polyorphonuclear neutrophiles, 4% were small lymphocytes, 3% were large lymphocytes, 38% were myelocytes, and 4% were eosinophiles. A diagnosis of myelogenous leukemia was made, and Blaud's pills, with Fowler's solution in increasing doses, was ordered. X-ray treatment was begun on December 7, 1903, commencing with daily exposures of 15 minutes each, gradually increasing to 20 minutes, using a medium high vacuum tube at an average distance of 10½ inches, the rays being confined to the area immediately over and about the spleen. A steady and progressive diminution in the size of the spleen was noticeable from the first. After 36 treatments the organ disappeared beneath the costal arch. Four weeks after treatment was begun a blood examination revealed 3,000,000 red cells, hemoglobin 60%, leucocytes 82,500. Differential: polymorphonuclears 77%, small lymphocytes 2%, large lymphocytes 1%, myelocytes 18%, eosinophiles 2%. Two weeks later (Jan. 17, 1904) the leucocytes had decreased to 52,000, though the actual number of myelocytes remained about the same. At this time the iron and arsenic were stopped, daily exposures of the X-ray being continued. January 31 (two weeks later) the red cells were 3,350,000, hemoglobin 65%, leucocytes 26,000, with polymorphonuclears 56%, small lymphocytes 15%, large lymphocytes 2%, meylocytes 24%, eosinophiles 3%. Urinalysis on the same date revealed no albumen, but a few hyaline casts and amorphous urates. On February 8, treatments were reduced to alternate days because of extreme bronzing and looseness of the skin over the splenic region, and continued so until the end.

Feb. 14, the red cells numbered 3,600,000, hemoglobin 70% leucocytes 15,000; polymorphonuclears 68%, small lymphosytes 8%, large lymphocytes 2%, myelocytes, 20%, eosinophiles 2%. Two weeks later the blood for the first time failed to show an improvement over the preceding count, the leucocytes numbering 19,000, the relative percentage of myelocytes remaining about the same. X-ray treatments were discontinued on February 20, and the last blood count (March 13) showed 3,600,000 red cells, hemoglobin 80%, leucocytes 12,600; polymorphonuclears 62%, small lymphocytes 20%, large lymphocytes 4%, myelocytes 12%, eosinophiles 2%.

He received in all 61 treatments. After the 36th treatment the spleen disappeared beneath the costal margin, and by the 45th treatment was normal in size and position. The liver had also decreased. He began to improve in his general condition from the beginning of treatment and the edema had entirely disappeared by the fourth week. His appetite has improved, his digestion is good, he sleeps well, and has had a gradual return of his strength. At present time he is able to return to his business, and claims to be stronger than at any time for the last two years.

It will be noticed that in case 3, which is symptomatically cured, and in case 2, which is improved, there has not been a great improvement in the red cells, the last blood count in the former showing 3,600,000, while in case 2 there has been an actual decrease, the red cells at the beginning of treatment numbering 4,200,000, while at the last examination they were only 3,680,000; the hemoglobin ratio has, however, decidedly improved.

The knowledge to be derived from the text books regarding the histogenesis of leucocytes is both fragmentary and misleading. Much confusion has arisen regarding the classification of leucocytes, and, in the light of the most recent investigations, we must discard preconceived ideas to a very large extent. Thus, the conception of the transition from young to old cells through small and large lymphocytes, polymorphonuclear neutrophiles, and eosinophiles, must give way in the light of the investigations of Pappenheim, Walz and Grawitz, Michaelis, Wolff, Taylor and others. To enter into a discussion of this work is beyond the confines of this paper, and after all we find these authorities at variance with each other to such an extent that our conception of the pathology of leukemia is for the present hopelessly tangled up. As a result of these investigations, however, the following theories may be presented:

(1). The large mononuclear leucocyte (larger than the large lymphocyte, from which it is further distinguished by having an eccentrically situated, pale, irregularly spheroid or ovid nucleus, and a relatively large amount of slightly basophilic, non-granular protoplasm) is the mother-cell, ordinarily capable of further differentiation into either the ordinary basophilic cell, or into a neutrophilic myelocyte.

(2) The two forms of leukemia, lymphatic and myelogenous, are closely associated, and are probably forms or stages of the same disease.

(3) Lymphocytes are formed in the lymphoid tissue of the bone marrow, and not exclusively in the lymph glands as formerly supposed.

(4) Myelocytes are formed in the bone marrow, and are the parent cells of the polymorphonuclear neutrophiles.

In myelogenous leukemia, myelocytes are cast into the blood circulation, in all probability, because of increased activity of the myeloid tissue of the marrow, which is the only tissue primarily affected in this disease.

Of course this conception of the pathology of the disease under consideration reduces the treatment here advanced to the role of empiricism, because the splenic enlargement is a result of the leukemia, and not the primary lesion. It is contended that this splenic enlargement can be accounted for because of the function of the spleen in its relation to erythrocytic hemolysis. This function has not been proven, however; and besides, we are confronted by the clincial results obtained by Senn, and more recently by Brown, who reports a case of myelogenous leukemia treated by X-ray for eight months with a return of the leucocytes and the spleen to normal. It cannot be argued that this result is due to medication, for Brown's patient, as well as Case 2 of my series, had no arsenic for the greater part of

the time. It would seem, therefore, that the X-ray penetrating the structures of the spleen or other tissue, was capable of producing tissue changes, which alter, temporarily, at least, the symptom-complex of this disease. The effect of the X-ray on the deeper structures, however, being to a great extent unknown, and as we are confronted by difficulties when we come to consider the etiology of the disease, equally as perplexing as those which meet us when considering its pathology, and as we know the tendency of this disease to improve and relapse at times entirely uninfluenced by any form of treatment, the note of warning sounded editorially by the *Journal of the American Medical Association* a week or two ago, is certainly both timely and necessary. Commenting on the cases reported by Senn and Brown, undoubted cases of the myelogenous type of leukemia, apparently cured by this treatment, it urges caution lest we prematurely call these cases permanently cured. On the other hand, we are now utilizing forces heretofore undreamed of, as therapeutic measures. These measures demand critical investigation on the part of the medical profession, and if they are to be kept out of the hands of the quack and charlatan, then scientific men must take them up.

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CONCRETIO-PERICARDII CUM CORDE.

(REPORT OF A CASE.)*

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THE following case, having several interesting features, was referred by Dr. W. H. Bergtold of Denver to Dr. Norman Bridge. In the absence of Dr. Bridge the patient was under my care for a period of three or four weeks, after which, and until the time of his death, he was looked after by us jointly. In referring the case Dr. Bergtold had made a diagnosis of "acute cardiac dilatation of two months' standing, with some improvement, but without complete compensation." After going carefully over the case I concurred in the diagnosis. The patient had been living for many years in Colorado, and much of the time at an altitude of 12,000 feet.

At my first examination, October 28, 1902, the patient, J. T. M., aged 49, gave a history of never having been ill, except a gonorrhea in youth, until two months previously, when at an altitude of 12,000 feet he had an attack of so-called "mountain fever" of a low type with which he had been in bed eighteen days. After the fever he became shortwinded, which was due, as he was told by his physician, to the fact that "the heart was stretched." This evidently was the supposed dilatation referred to. He went to a lower altitude in Colorado, and was much improved, but never wholly free from dyspnea, after which he returned to an altitude of 12,000 feet and became much worse by exercising.

At the time of my examination, October 28, 1902, he complained of severe dyspnea, indigestion and general weakness. His weight was 175 pounds, some twelve pounds above normal. His temperature was 97½; pulse not countable at the wrist; respiration somewhat accelerated and shallow. Physical examination revealed an enlargement of the cardiac area. The heart sounds were very feeble, but with no valvular murmur. The liver was considerably enlarged. The urine was normal in quality and quantity.

The patient was sent to the California Hospital and put to bed for three weeks, during which time he had occasional attacks of dyspnea, with a disturbed digestion, but was otherwise fairly comfortable, and during this time showed very considerable improvement. During these three weeks there was no elevation of temperature, no cough or expectoration, and several careful examinations of the chest were made without suspicion of tuberculosis. After leaving the hospital he secured quarters with a friend in the suburbs of Los Angeles, and appeared at the office occasionally.

The subsequent history of his case until his death, upon December 18th, was one of increasing dyspnea, with a gradual development of edema of the lower extremities, gradually extending to the lower portion of the trunk and the left pleural cavity. He died a rather distressing death, with the ordinary symptoms of a gradual weakening heart. Albumin and casts became abundant in the urine some time before death.

The following were the postmortem findings as made by Dr. Stanley P. Black:

"The lungs presented small tubercles submiliary in size, scattered throughout cut surface, with occasional areas of old caseation. The pericardial sac was entirely obliterated by adhesions and great thickening. This cicatricial tissue showed microscopically a chronic tuberculosis, with extensive areas of caseation and tubercles surrounding these areas. The heart showed brown atrophy. Liver somewhat enlarged, and on section nutmeg in appearance. Microscopically the typical findings of chronic passive congestion. The spleen showed slight hyperplasia of splenic pulp. Kidneys somewhat enlarged and soft, microscopically showing cloudy swelling and some degeneration of the tubular epithelium."

Diagnosis.—Submiliary tuberculosis of lungs; chronic adhesive pericarditis (tuberculous), (*concretio-pericardii cum corde*); chronic passive congestion of the liver.

Some of the points of interest in the case are as follows: As noticed by the patient, his only illness during life, other than his attack of gonorrhea in youth, was one of eighteen days duration, said to have been "mountain fever," occurring four months previous to his demise. This may have been the pericarditis resulting in complete adhesions. During the three weeks of careful observation while in the hospital, two months after his so-called "mountain fever" and five weeks previous to his death, he had a regular and constant morning temperature of 97.6 degrees, with an evening temperature of 98.4, notwithstanding an active pulmonary tuberculous process. At this time the pulse rate was variable, from 76 to 108, and at times almost inappreciable at the wrist. The heart, while showing brown atrophy at the postmortem, gave the physical signs of cardiac dilatation, with enlarged cardiac area. This was due to the enormously thickened pericardial layers, which were firmly adherent.

DISCUSSION.

Dr. H. G. Brainerd, Los Angeles.—The case reported by Dr. Cole is unlike any I have ever seen. I am not always allowed to make autopsies on some very interesting cases, otherwise I might have found this condition. But as it is, I have never seen anything like it.

Dr. George H. Evans, San Francisco.—These cases are very rare. There is one thing that Dr. Cole did not mention in the clinical history, and that is what can be gained on inspection. I saw quite a number of these cases in a small hospital, and in every instance, on inspection, there is a very prominent tranverse wave impulse. These patients have invariably very much enlarged hearts.

Dr. George Blumer, San Francisco.—These cases are very often taken for valvular heart disease. There is a dilatation of the heart, with a relative insufficiency of the valve. A good many of these cases simulate cirrhosis of the liver, so-called pericardial

*Read at the thirty-fourth annual meeting of the State Society, Paso Robles, April 19-21, 1904.